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EDITORIAL

Giving something back to the authors

For centuries scientific publishing has worked on a bizarre economic model: the real producers of the raw material, the researchers, have received no direct payment for their work. In return for publication they have received exposure, "findability" (thanks to bibliographical databases provided by others), and the "imprimatur" of peer review. Because peer review is an imperfect process,[1] exposure and findability are probably the more important benefits. For their part publishers have largely borne the costs of funding peer review systems and of providing the exposure, and in return they have controlled all the rights to their authors' work and taken all the cash. That has been as true of professional association publishers as it has been of commercial ones: the professional associations can argue that their surpluses have helped to support the work of the associations and their members, but individual researchers have not received any direct monetary reward for their labours. This *Journal* is now proposing to share some of the cash from commercial reprint sales with its authors. We also hope that we can use the part that we don't share with them to increase something that may matter more to them—exposure.

This proposal has arisen in part from a closer look at our copyright agreements with authors. Like most publishers we have traditionally asked authors to assign their copyright to us. This has been done so that we can exploit those rights ourselves, and tackle infringements, without having to go back to each author each time. We have also made money out of allowing third parties such as pharmaceutical companies to reprint those articles or translate and distribute them. In practice we have always allowed authors themselves to use their material freely in other publications (such as multiauthor books) and for their own teaching and research purposes without charge. However, recently some authors have become resentful of the fact that publishers take all their rights, often don't exploit them well, and then insist that they ask permission when authors want to use their own material themselves.

We have therefore decided that we will no longer ask authors to assign their copyrights. Instead we will ask for an exclusive licence. In practice, as several authors have pointed out, this gives us almost the same control as we had before, but we have also undertaken to allow the rights to revert if we haven't exploited them in the print *JNNP* or the *eJNNP* within a year, and in addition authors will no longer have to ask us for permission to use their material for any non-commercial use. Thus if they want to photocopy or download their own article to distribute among their students or place it as a chapter in a multiauthor work (non-commercial product) they can do so without asking; similarly, they can post a copy of their own article on their own or their institution's website.

We also propose to give our authors 10% of the revenue we make when we sell a reprint order or a translation right worth more than £1000. We will therefore ask authors to nominate someone, or some organisation—the research group or department—to receive any payments. Our reasons for not paying out on smaller orders is because the administration costs would be disproportionately high, and our reasons for not giving more than a small percentage is because we need the revenue to help fund publication of the *Journal*. Although we hope that sharing our reprint revenue might help pay something back to the scientific community which we serve and on which we depend, we think that we can best keep our contract with authors by working hard to increase their exposure.

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EDITORIAL

Recent progress in drug treatment for acute stroke

The publication of the positive results of the National Institutes of Neurological Disease and Stroke (NINDS)[1] trial of alteplase (a recombinant tissue plasminogen activator) for patients with acute stroke in 1995 and its approval by the US Food and Drug Administration as well as by the American Academy of Neurology and American Heart Association[2 3] increased the interest and attention of the medical community for acute stroke treatment. However, the implication of this NINDS Stroke Study and other thrombolytic trials in clinical practice remains extremely controversial and debated. Furthermore, the recent publication of the results from the European Cooperative Acute Stroke Study II (ECASS II)[4] will feed the controversy as ECASS II[4] results are disappointing and do not confirm the positive results of the NINDS Stroke Study.[1] Consequently, what is the more reasonable position concerning thrombolysis by alteplase, and what seems to work has not been established yet beyond reasonable doubt. Numerous trials devoted to neuroprotection against acute ischaemic stroke have been prematurely stopped because of safety concerns or poor risk:benefit ratios, but some new neuroprotective drugs seem promising and are being tested. The third area of research in progress is the use of antithrombotic drugs in the acute phase of stroke. In this paper, we review selected recent clinical trials focusing on recent advances in acute stroke therapy.

Thrombolytic therapy

The recent publication of the neutral results of the European Cooperative Acute Stroke Study II (ECASS II)[4] in October 1998, did not confirm the positive results of the NINDS Stroke Study[1] and constitutes a great problem for people who wanted to obtain a rapid licensing of alteplase in Europe as well as the recognition that alteplase was a treatment for acute ischaemic stroke. ECASS II[4] was designed to test whether intravenous alteplase (rtPA), given within 6 hours of proved acute ischaemic stroke, could increase the proportion of patients having a "favourable outcome" at 3 months, estimated by the modified Rankin scale score of 0 or 1. The dose of alteplase used in ECASS II[4] was the same as for the NINDS Stroke Study[1]—0.9 mg/kg bodyweight with an upper dose limit of 90 mg/patient (a bolus of 10% of the total dose was given over 1–2 minutes, followed by a 60 minute intravenous infusion of the remaining dose)—to match NINDS criteria. Eight hundred patients were enrolled in ECASS II, which was a non-angiographic, randomised, double blind trial; 409 patients received alteplase whereas 391 were randomly designed to have placebo. Alteplase increased the proportion of "favourable outcome" from 36.6% to 40.3%, a non-significant absolute increase of 3.7% (p=0.277). However, in a post hoc analysis of modified Rankin scale scores dichotomised for death or dependency, a favourable outcome was found in 54.3% of alteplase group patients and in 46.0% of placebo group patients, a significant absolute difference of 8.3% (p=0.024).[5] By comparison, the absolute benefit for a "favourable outcome" (mRS=0 or 1) (16.2%) was significant in the NINDS Stroke Study[1] and non-significant (6.4%) in ECASS I.[5] If we consider only the first results of ECASS II[4] (without the post hoc dichotomised analysis), the two ECASS studies[4 5] produce the same neutral results. ECASS II[4] showed no evidence that efficacy of intravenous alteplase treatment depends on administration within 3 hours of symptom onset. Indeed, there were no significant differences between the alteplase and placebo groups according to time strata of 0–3 hours and 3–6 hours of stroke onset, although it was not powered to show such a difference (only 158 patients in the 0–3 hours subgroup). The overall mortality rates at 3 months were much lower in ECASS II[4] (10.5% in alteplase group *v* 10.7% in placebo group) than in ECASS I[5] (22.4% *v* 15.8%) or the NINDS Stroke Study[1] (17.3% *v* 20.5%), whereas the rate of symptomatic intracranial haemorrhage was 8.8 % (3.4% in the placebo group) *v* 6.4% (0.6% in the placebo group) in ECASS II[4] and NINDS trials,[1] respectively. The ECASS II study group[4] reported that intracranial haemorrhages did not lead to an overall increase in morbidity or mortality in the alteplase group. In conclusion, ECASS II[4] seems an equivocal study—negative for the primary end point (mRS=0 or 1) and positive for post hoc analysis of modified Rankin scale scores dichotomised for death or dependency (mRS=0, 1, or 2 classified as favourable)—and must be interpreted with caution for several reasons.[6] Firstly, stroke patients randomised in ECASS II[4] had less severe neurological deficits at entry to the study, which can represent a possible selection bias; the median baseline NIHSS scores in the alteplase and placebo groups were 13 and 12 in ECASS I,[5] 14, and 15 in the NINDS trial,[1] and 11 in both groups in ECASS II.[4] Moreover, in ECASS II,[4] patients showed fewer signs of early major infarction on baseline CT, presumably as a result of better CT surveillance. Consequently, ECASS II[4] was characterised by a higher number of patients with mild stroke recruited which can explain why a better placebo response and a lower mortality rate were found in ECASS II[4] by comparison with ECASS I[5] or the NINDS trial.[1] Patients with mild stroke are probably less likely to benefit from thrombolysis than those with more severe stroke as many will improve spontaneously. This finding suggests that we need more knowledge about predicting factors of spontaneous recovery as well as about the vascular status of the individual patient (artery occluded or not). ECASS II, ECASS I, and the NINDS trial are non-angiographic studies. Secondly, the primary end point reflecting a "favourable outcome" is uncommon in stroke trials, which normally base it on independence (Rankin scale score of 0–2). Of interest is that the post hoc analysis of ECASS II becomes positive when analysed with independence as the outcome (absolute benefit of 8.3%; p=0.024). Thirdly, as for ECASS I[5] and the NINDS trial,[1] ECASS II[4] is insufficient in terms of number of patients to keep a power significance because the thrombolytic studies do not take into account the great heterogeneity of stroke (aetiology, mechanism, prognosis). Additionally, it is important to compare the response to thrombolytic therapy according to the aetiology of stroke, as described in the NINDS trial.[1] In this trial, it was the lacunar stroke subgroup which

paradoxically demonstrated the best response to rtPA treatment. Additional studies with alteplase including over 1500 patients would be useful to recruit a sufficient number of patients in each subtype of stroke. Because of the margin between the probability of decreasing the likelihood of disability by 12% and the increased probability of death by 5% over placebo[7] and because it is currently impossible to predict which patient would be affected by a symptomatic intracranial haemorrhage[6]— the rate of intracranial haemorrhage is strongly increased by alteplase—we think that it is premature to consider alteplase as a therapy to be applied in most cases of routine clinical practice. Much more data are crucial to identify which patients will more likely benefit from thrombolysis and which patients will be more at risk for it. Failure to better understand this issue constitutes a major limitation to the implementation of alteplase in general practice for individual patients with acute stroke. Selection to keep patients with the best risk to benefit ratio with alteplase should lead to a better understanding of: (1) the most appropriate time window. This was less than 3 hours in the NINDS trial,[1] whereas ECASS II[4] and post hoc analysis of ECASS I[8] suggest that the time window for thrombolysis may be as long as 6 hours. For instance, to recruit 624 patients in the NINDS trial within the 3 hour interval, investigators had to screen about 16 000 patients[9] whereas only one in five patients would be treated within 3 hours of stroke onset in ECASS II.[4] (2) Predictor factors of spontaneous recovery from stroke and definition criteria to identify patients with a mild stroke for whom the risk to benefit ratio is smaller. (3) Predictors of brain haemorrhage. As far as the three trials devoted to the use of streptokinase in acute stroke treatment are concerned (MAST-E,[10] MAST-I,[11] and ASK[12]) the classic view is that streptokinase (no significant difference for the primary end point of "unfavourable outcome") is ineffective and dangerous because all these three studies showed an increased hazard related to intracranial haemorrhage. However, on the one hand, there is no study focusing on the direct comparison between streptokinase and alteplase, and on the other, streptokinase has not been adequately tested by dose ranging studies, unlike those of alteplase. Consequently, the common streptokinase dose, 1.5 MU, might be excessive, which can explain the increased rate of intracranial haemorrhage (leading to a premature interruption of the ASK study).[12] Moreover, the Cochrane systemic review[13] of thrombolytic studies provides indirect evidence that aspirin might increase the risk of ICH in the presence of alteplase or streptokinase. Recently, a new trial ATLANTIS (Alteplase Thrombolysis of Acute Noninterventional Therapy in Ischemic Stroke), which was a placebo controlled, double bind pivotal study of the use of alteplase in patients with acute ischaemic stroke 3 to 5 hours from symptom onset, has been considered as a negative trial. The results of the PROACT-II study (Prolyse in Acute Cerebral Thromboembolism Trial) in which the dose of the pro-urokinase injected into the middle cerebral artery was 9 mg (6 mg pro-urokinase in the PROACT-I study) showed significant clinical benefits of performing an intra-arterial thrombolysis in patients with an acute ischaemic stroke in the middle cerebral artery territory.

We think that thrombolysis is a potentially effective therapy for acute stroke[14 15] but additional information is necessary to establish how to select the best candidates for alteplase treatment before using it routinely, even within 3 hours of stroke onset.

Neuroprotective drugs

Despite numerous agents which can prevent the excitatory cascade of events leading to ischaemic neuronal death in experimental conditions, there is still no neuroprotective agent that has been shown conclusively to improve stroke outcome. A plethora of cellular and molecular mechanisms such as free radical production, lipid peroxidation, excitotoxicity, and calcium ion (Ca^{2+}) overload constitute the important therapeutic targets of neuroprotection and it is now known that interventions such as delivering neuroprotective agents can participate to salvage a potentially reversible ischaemic region known as the ischaemic penumbra.

The first neuroprotective agent tested in stroke patients was nimodipine. This compound, a dihydropyridine, has been the most widely tested neuroprotector and provided no benefit in 15 trials[16] involving 5320 patients but a meta-analysis of the nine major nimodipine trials,[17] comprising 3719 patients, showed a significant improvement in functional outcome for those who received nimodipine within 12 hours of stroke onset. Nevertheless, the Intravenous Nimodipine West European Stroke Trial (INWEST)[18] trial with intravenous nimodipine doses of 2 mg/hour has shown that under some conditions, nimodipine may be harmful.This was suggested by an increased mortality, directly correlated with a fall in blood pressure. The second class of neuroprotective drugs is represented by the N-methyl-D-aspartate (NMDA)-receptor antagonists which inhibit the action of glutamate—the major excitatory neurotransmitter of the brain—excessively released from presynaptic neurons by ischaemic injury of the brain. The NMDA receptor, a well characterised receptor mediated calcium channel, also contains glycine and polyamine modulatory sites that are potential therapeutic targets for neuroprotection. The inhibition of glutamate activated receptors which operate Ca^{2+} channels has been the focus of several phase II and III trials of different drugs proved to reduce the size of ischaemic lesions in animals. Clinical trials, with competitive— selfotel[19]— and non-competitive—aptiganel,[20] dextrorphan[21 22]— NMDA receptor antagonists have been stopped because of safety concerns or poor risk:benefit ratio. Glutamate antagonists share a propensity to cause psychotomimetic effects.[1] Two phase 3 trials of eliprodil,[23 24] an antagonist at the polyamine site of the NMDA receptor, were also stopped, due to a lack of efficacy in interim analyses. Moreover, eliprodil may potentially cause ECG effects (QT prolongation). A new potent antagonist at the glycine site of the NMDA receptor, GV150526, has just been tried in a phase II study in patients with acute stroke.[24] This antagonist was generally well tolerated and there was no excess of adverse events in the CNS. A phase III trial is under way. Lubeluzole, a benzothiazole compound, is a sodium channel blocker that may inhibit the release of glutamate from ischaemic neurons, reducing postsynaptic excitotoxicity,[16] but it may act through other mechanisms as well, which include inhibition of glutamate induced nitric oxide (NO) related toxicity, with normalisation of peri-infarct neuronal excitability.[24] This corresponds to an NO synthase modulating effect. Three phase 3 placebo controlled trials testing lubeluzole with mortality as the primary end point have been completed, including 1375 patients within 6 hours of stroke onset.[25 26] Lubeluzole was given at a dose of 7.5 mg over 1 hour followed by 10 mg/day for up to 5 days. The European trial[27] was negative, whereas a non-significant trend for decreased mortality and a small significant effect on functional outcome was shown in the United States trial.[25] Combined results suggested a positive effect in mild to moderate—but not severe—stroke. A large phase III study to test the efficacy and safety of lubeluzole in the treatment of acute ischaemic stroke—with an 8 hour time window—has failed to show efficacy. As with eliprodil, an occasional but transient QT

prolongation on ECG was seen. The rationale for using the antioxidants—free radical scavengers—is that ischaemia induces release of highly reactive oxygen free radicals, which are toxic to membranes. A 21aminosteroid tirilazad mesylate has free radical scavenging activity and antioxidant effects. Tirilazad has been evaluated in 1757 patients from six stroke trials. The most recent phase 3 trials with increased tirilazad dosage were stopped because of safety concerns or because they were unlikely to be of benefit.[24 26] There are contradictory findings; in the European-Australian study (TESS II), mortality with tirilazad was 10.5% at 10 days (5% with placebo) and 18% at 3 months (14% with placebo) whereas in the United States-Canadian study (RANTASS),[28] mortality with tirilazad was 11.5% at 10 days (14% with placebo) and 19% at 3 months (38% with placebo). However, analysis of 111 patients enrolled in the high dose study in North America (RANTASS II)[29]—prematurely stopped when questions regarding safety emerged from TESS II—showed an absolute reduction in mortality of 14% and an increase in the proportion of patients who were independent at 3 months. However, the differences were not significant. Another potential neuroprotective agent is ebselen, a seleno-organic compound with antioxidant activity through a glutathione peroxidase-like action. Ebselen seems to increase the functional outcome but the improvement is significant only if the drug is received within 24 hours of stroke onset.[30] Another approach consists of developing γ-amino-butyric acid (GABA) agonists because GABA is the major inhibitory neurotransmitter receptor in the brain and can balance the excitatory effects of glutamate. A recent phase III trial (Clomethiazole Acute Stroke Study (CLASS)), in which 1354 patients received placebo or 75 mg/kg clomethiazole—which has an effect on $GABA_A$ receptors (gate a chloride channel)—for 24 hours within 12 hours of stroke, showed no overall benefit, but there was a significant (37%) improvement in functional outcome in the subgroup of patients with large or cortical strokes.[31] A new trial has now been targeted at this subgroup and will include 1200 patients. Furthermore, data suggest that 5-clomethiazole is safe even in patients with haemorrhagic stroke.[32] These findings will be further investigated in a prospectively designed trial which is ongoing in the United States and Canada (Clomethiazole Acute Stroke Study-H (CLASS-H)).[32] Based on the role of neutrophils in the development of cerebral infarction as well as their mediation in some aspects of reperfusion injury,[26 33] the administration of anti-intercellular adhesion molecule (anti-ICAM) antibodies directed at neutrophils has been tested in patients with acute stroke. Enlimomab, a monoclonal antibody, was given intravenously within 6 hours ((160 mg (day 1) followed by 40 mg/day (days 2 to 5)) in a placebo controlled phase III trial[34] which included 625 patients. The results were negative, with worse outcome and increased mortality in the treatment group, in relation to increased infections and fever.[16 34] Because piracetam has been found to be present in the phospholipid membrane models and this probably accounts for the maintenance or improvement of membrane bound cell functions including ATP production, neurotransmission, and secondary messenger activity, a study was planned to investigate the potential therapeutic effect of piracetam in acute stroke. In a phase 3 trial,[35] 927 patients were randomised within 12 hours to piracetam (12 g as an initial intravenous bolus, 12 g daily for 4 weeks, and 4.8 g daily for 8 weeks) or placebo, with no difference in functional and neurological outcome. However, a trend toward improvement of the neurological score was found in the subgroup of patients randomised within 7 hours of onset, particularly in patients with stroke of moderate and severe degree. A new randomised, placebo controlled, multicentre trial with a 7 hour window is now being launched (PASS II). Citicoline (cytidine-5'-diphosphocholine), which is a precursor of phosphatidylcholine contained in neural cell membranes, has antioxidant properties, and promotes brain acetylcholine synthesis as a repairing agent. During ischaemia phosphatidylcholine is separated into free fatty acids, which can then generate free radicals that potentiate ischaemic injury. Although it is often presented as a neuroprotector, it may rather act on recovery through delayed restorative mechanisms. Two trials,[36 37] one in 259 patients, the other in 394 patients, have triggered some interest in this drug, which showed no safety problem. The drug was given orally for several weeks within 24 hours of stroke onset, which clearly distinguishes these trials from usual acute stroke trials. A significant improvement in functional outcome was claimed at 3 months in the treated group, but apparently this was the case only in subgroups of patients (mainly the 500 mg subgroup; moderate to severe strokes). Basic fibroblast growth factor (bFGF), insulin-like growth factor, brain derived neurotrophic factor, and osteogenic protein 1 are among growth factors with a potential interest for stroke trials.[33] A specific interest is that they may have both acute phase effects and an action on recovery by reinforcing plasticity phenomena. In animal experiments, an improvement in outcome has been found even with delayed treatment (24 hours) despite a lack of reduction of infarct size. A recently completed phase 2 trial showed that bFGF was well tolerated by stroke patients but phase 3 trials have been interrupted for safety or concerns over lack of benefit. Finally, numerous other neuroprotective drugs with potential clinical interest including nitric oxide synthase inhibitors (ARL17477); cell cycle genes involved in apoptosis; immediate early genes (protooncogenes, c-fos, c-jun, etc); heat shock proteins; and trophic factors which may reduce programmed cellular death; a potent and specific opener of large conductance calcium activated (maxi-K) potassium channels ((S)-BMS-204352 for (S)-3-(5-chloro-2-methoxyphenyl)-3-fluoro-1,3-dihydro-6-(trifluoromethyl)-2H-indol-2-one); a serotonin agonist (Bay 3702)[38]; and magnesium (Mg^{2+}) which blocks the voltage dependent ion channel of the NMDA-receptor complex, and also acts as a non-competitive NMDA-receptor antagonist at higher doses. Magnesium may block the influx of calcium into ischaemic neurons. The Intravenous Magnesium Efficacy Study in Stroke (IMAGES)[16 39 40] is ongoing.

Several authors[41–44] have shown that hyperthermia (>37.5°C) was associated with a worse prognosis. Although no randomised clinical trials of therapeutic hypothermia in acute ischaemic stroke have yet been announced to establish the efficacy and safety of this therapy, encouraging results have been recorded recently in acute traumatic brain injury. In the interim between studies, some authors[45] think that available evidence is sufficient to recommend to maintain body temperature in a safe normothermic range (36.7°C to 37°C), for at least the first several days after acute stroke. Moreover, in a very recently published study, Schwab *et al*[46] showed that moderate hypothermia—patients were kept at 38°C body core temperature for 48 to 72 hours—in patients with severe ischaemic stroke can help to control critically increased intracranial pressure values in severe space occupying oedema after middle cerebral artery stroke and may improve clinical outcome with no severe side effects.

In general, it is striking how drugs which have been shown to decrease significantly the size of infarct in animal models are not found to be clinically efficient in stroke patients.[33 47 48] Nevertheless, promising results have been obtained with new neuroprotective drugs such as

GV150526, ebselen, glycine site antagonists, clomethiazole, fos-phenytoin, bFGF, NO synthase inhibitors, and BAY 3702,[38] for which further studies are underway to confirm the preliminary results. The discrepancy between experimental and clinical results for neuroprotective drugs may be due to several factors: the marked heterogeneity (aetiology, mechanism) of human stroke, better control of biological variables in specimens, and the use of different time windows. Indeed, most of the earlier clinical trials were performed with a time window greater than 24 hours, which was most often arbitrarily fixed; even an efficient drug cannot possibly be demonstrated to have a positive effect under these conditions.

Questions remain concerning the effective concentration of neuroprotective drug reached in the cerebral ischaemic infarct if the artery supplying this territory is occluded. Should a thrombolytic agent be administered with the neuroprotective drug in a "cocktail" to increase the effective concentration of the neuroprotective drug in the ischaemic region? We think that knowledge of the vascular status of the stroke patient is crucial to determine the best therapeutic strategy. Another problem that may hamper our ability to achieve neuroprotection in stroke patients is a relative lack of understanding of specific pathophysiological issues of brain ischaemia in relation to the modes of action of specific drugs. For instance, antioxidants experimentally have an effect only in temporary focal ischaemia models, which suggests that their main clinical application would be in association with agents that facilitate reperfusion (thrombolytic drugs). Also, certain classes of neuroprotective drugs, which act on specific synapses and receptors, may not work in white matter ischaemia, because these synapses and receptors may be malfunctional in such a situation or because these synapses and receptors—such as NMDA receptors—are lacking in the white matter. Indeed, in stroke patients, glutamate seems to be a marker for cortical but not for deep hemispheric ischaemia. On the other hand, NMDA receptor antagonists may be particularly appropriate in patients in whom glutamate concentrations rise markedly, such as in progressive ischaemic stroke.

Several critical issues remain unsettled for neuroprotection. Firstly, the duration of treatment that would achieve the best effect is unknown, and is probably different for different drugs. The phase of locally reduced flow is present in 100% of patients scanned within 9 hours and drops to 30% within 4 days with ischaemia, but viable tissue may be seen up to 48 hours after onset of stroke.[49] Consequently, there is a rationale for starting and continuing neuroprotection for up to a least 48 hours after stroke onset. Perhaps neuroprotection should be given for several days or weeks after the first clinical cerebrovascular event, which is the period in which the risk of recurrence is the highest. A second critical issue for neuroprotection is that the interaction and influence between neuroprotective drugs and physiological variables (blood pressure, temperature) as well as with common drugs used in neurology are usually not taken into account. On the one hand, it is well established that benzodiazepines, neuroloptic drugs, antihypertensive drugs (clonidine, prazosin), phenytoin, phenobarbital, and other drugs may modulate the effect of neuroprotecting agents. On the other hand, treatments which act on blood pressure concentrations, mainly in limiting variations and falls, are usually not included among neuroprotecting strategies.

Antithrombotic drugs

The rationale for early anticoagulant therapy in acute ischaemic stroke is not consensual. Anticoagulants do not recanalise occluded arteries and do not have neuroprotective effects. However, they may be useful in preventing progression of thrombosis and early recurrences of embolic stroke. The use of high doses (20 000 U/24 h) of intravenous heparin followed by oral anticoagulant therapy is well accepted in the medical community as treatment shortly after ischaemic stroke in patients with a cardiac source of embolism or rarer disorders, such as the antiphospholipid antibody syndrome. However, there is no consensus on the time to start anticoagulant therapy, because of the early risk of haemorrhagic transformation in the ischaemic area. This decision is usually individual and empirical, based on the severity of brain ischaemia (increased risk of bleeding) and the risk of early recurrence of stroke. Two other conditions are commonly associated with the early administration of full dose intravenous heparin, progressing ischaemic stroke, and crescendo transient ischaemic attack (usually due to developing lacunar infarction).[50] However, there is no randomised evidence of benefit of giving these patients anticoagulants.

The concept of intravenous heparin therapy shortly after ischaemic stroke was recently considered in the International Stroke Trial (IST),[51] an open randomised megatrial with a factorial design (intravenous heparin (10 000 U or 25 000 U/day *v* not); aspirin (300 mg/day *v* not)); 19 435 patients from 467 hospitals were randomised within 48 hours of stroke onset. Primary outcomes (death<14 days; death or dependency at 6 months) showed no difference with or without heparin. Recurrent ischaemic stroke at 14 days showed a significant 0.9% absolute risk reduction with heparin, which was counterbalanced by a significant 0.8% absolute increased risk for haemorrhagic stroke. Haemorrhagic complications (transfused or fatal extracranial bleeds, haemorrhagic stroke) were associated with the high dose heparin regimes. On the other hand, the low dose heparin regimen showed encouraging findings, with a significant 1.2% absolute decrease in risk of death or non-fatal recurrent stroke at 14 days, with haemorrhagic complications in the same range as with aspirin. Although the authors[51] advised against the early use of heparin after ischaemic stroke, these findings with the low dose regimen may in fact comfort the numerous clinicians who have been giving it for years. Moreover, brain CT was not required before starting therapy, and no coagulation monitoring was required either, which imply considerable biases against heparin. For these reasons, many clinicians who were giving low dose heparin (usually subcutaneously) as a prophylaxis of stroke complications, or even high dose intravenous heparin have not changed their practice as a result of the IST results.[51]

Another potential antithrombotic drug is the low molecular weight heparin (LMWH) which has been investigated in the study of Kay *et al*. In this study,[52] 312 patients were randomised to placebo or nadroparin (4100 anti-factor Xa units once or twice a day for 10 days) within 2 days of stroke onset. Death or dependency at 3 months was 45% in the 8200 U/day dose, 52% in the 4100 U/day dose, and 65% in the placebo group (p=0.005). However, there was no difference for death, haemorrhagic transformation, or complications at 10 days. This is strange, as LMWH is expected to prevent early stroke complications or recurrences, not to selectively improve late outcome. Indeed, a recent overview of available trials concluded that LMWH may constitute the best prophylaxis of deep venous thrombosis for patients with ischaemic stroke, although a direct comparison with low dose unfractionated heparin is not available in this condition.

The only randomised experience in acute stroke with the low molecular weight heparinoid Org 10172 (danaparoid) has been reported by the TOAST[53 54] investigators. In this double blind placebo controlled trial, 1281 patients were

treated within 24 hours of stroke onset over a 6 year period. Patients with a Glasgow outcome scale I or II and whose Barthel index was >12/20 were judged to have a favourable outcome. At seven days 376/635 (59%) patients who received the heparinoid *v* 344/633 (54%) controls had a favourable outcome (p=0.072). This trend to benefit in treated patients was absent at 3 months (482/639 (75%) *v* 467/633 (74%) p=0.06). Subgroup analyses suggested that patients with disease of the large arteries may have improved benefit, and that use of aspirin in the week before the onset of stroke was associated with less severe neurological impairment. After the overall disappointing results of TOAST were known, an ongoing European study (EURO-TOAST) was stopped. This low molecular weight heparinoid ORG10172 (danaparoid sodium) is not associated with an improvement in favourable outcome at 3 months, despite an apparent positive response to treatment at 7 days.[54]

Finally, the therapeutic impact of aspirin in the acute phase of stroke has recently been evaluated in two megastudies. The International Stroke Trial (IST) and CAST trial including over 40 000 patients randomised to aspirin *v* not within 48 hours of stroke onset were recently published.The IST[5] evaluated aspirin (300 mg/day) and heparin (10 000 or 25 000 U/day) in a factorial design; 19 435 patients were included from 467 hospitals. Treatment was given for 2 weeks. Both primary end points (mortality at 2 weeks (9%) and mortality or severe disability at 6 months (63%)) were not statistically different between the aspirin, heparin, and placebo groups. Despite this global negativity, it must be emphasised that secondary analyses showed a significant decrease at 2 weeks of recurrence of ischaemic stroke (2.9% *v* 3.8%) and of combined mortality plus non-fatal recurrent stroke (11.3% *v* 12.4%) with aspirin. Aspirin was associated with 5/1000 more transfused of fatal extracranial haemorrhages, whereas haemorrhagic stroke at 2 weeks was not significantly increased (0.9%).

In the Chinese Acute Stroke Trial (CAST),[55] aspirin (160 mg/day) or placebo was given for 4 weeks to 21 106 patients from 416 hospitals. Mortality at 1 month was slightly but significantly decreased with aspirin (3.3% *v* 3.9%), without decrease in combined mortality or severe disability. As in the IST trial,[51] secondary end points showed significant benefit from aspirin, including a decrease in recurrence of ischaemic stroke (1.6% *v* 2.1% at 1 month) and in combined mortality plus non-fatal stroke (5.3% *v* 5.9% at 1 month). A combined analysis of IST and CAST data suggested that one death, myocardial infarct, or new stroke can be avoided by giving aspirin to 100 patients with acute stroke. It must be emphasised that the prescription of aspirin starting at the time of admission was already considered part of best care in many centres around the world, even before IST of CAST were launched, so that the results of these trials may have modified practice only in the centres where the benefit of aspirin was considered uncertain, which may mainly correspond to the IST and CAST participants themselves. In any case, aspirin should not be regarded as an acute stroke treatment, but rather as an early preventive therapy in acute stroke.

New avenues of antithrombotic therapy in acute stroke may be provided by antiglycoprotein GIIb/IIIa receptor antagonists, which have shown a favourable risk to benefit ratio in myocardial infarction and unstable angina.[56 57] A recent dose escalation study of abciximab in acute ischaemia stroke showed no safety or toxicity concern, and a phase II trial is being launched. Finally, ancrod, which is a thrombin-like defibrinogenating agent that converts fibrinogen into soluble fibrin products, with subsequent decrease in fibrinogen concentration and plasma viscosity, has been shown to benefit patients with acute ischaemic stroke.

Conclusions

Studies of thrombolytic, neuroprotective, anticoagulant, and antiaggregant drugs currently dominate the field of acute stroke treatment. Crucial information has been obtained on the efficacy and safety of new drugs as well as combined therapy (synergistic drug effects). Advances in stroke therapy will shortly improve the consequences of this potentially devastating but newly treatable disorder.

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EDITORIAL COMMENTARY

Homeostatic effects of carotid stenosis

Signalling of blood pressure changes is partly the result of carotid sinus function and activity within the afferent glossopharyngeal and vagus nerves. Carotid stenosis is common and often affects the carotid bulb where the arterial baroreceptors are situated. However, little attention has been paid to the homeostatic effects of stenosis at this point. Akinola *et al* in this issue (pp 428–32)[1] compare autonomic reflexes in a group of hypertensive patients with transient ischaemic attacks (TIAs) and unilateral or bilateral carotid stenosis to matched groups of hypertensive and normotensive controls. Their findings indicate that baroreflex sensitivity is blunted, the effects being equal in patients with either unilateral or bilateral carotid stenosis compared with both control groups. In other respects, autonomic reflexes are blunted to the same extent as seen in hypertensive controls, indicating no specific involvement of cardiovascular efferents in the stenosis group. There are two main caveats. The first concerns the use of antihypertensive medication. Such treatment, especially with angiotensin converting enzyme activators (which may act on AT receptors in the area postrema) or β-blockers can affect baroreflex sensitivity. Although these medications were stopped within 1 day of the study, their central effects may be longer lasting. Secondly, other mechanoreceptors in the left ventricle and aortic arch may be intact in these patients. However, the shrewd use of a hypertensive control group on similar medication to some extent allays some of the interpretative complications. Why the effects are similar in patients with severe unilateral and bilateral carotid stenosis is a matter of conjecture. This could indicate a complex non-linear compensatory effect within the brain, using baroreceptor input from the aortic arch and other regions. The importance of this study is threefold: firstly, such patients may be at risk of presyncopal symptoms which may be erroneously diagnosed as focal brainstem transient ischaemic attacks; secondly, impaired peripheral blood pressure regulation could affect cerebral blood flow in the post-stroke state as such patients lose cerebral autoregulation. The effects could also be accentuated in patients with tandem intracranial stenosis. Finally, it should not be forgotten that control of blood pressure may be impaired after carotid endarterectomy and the effects of antihypertensive medication in these patients should be monitored most carefully.

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EDITORIAL COMMENTARY

Resurgence of diphtheria in the newly independent states of the former Soviet Union: a reminder of risk

The introduction of universal childhood immunisation programmes with diphtheria toxoid in the 1950s has led to virtual elimination of diphtheria from most developed countries. In the past, the highly contagious acute infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae* had endangered in particular children of preschool age. Given a case fatality rate of 5% to 10%, diphtheria had been considered one of the most serious communicable diseases of childhood. The practice of routine mass immunisation of children resulted in a dramatic decline of incidence and mortality from diphtheria in many European countries, including the former Soviet Union where, by 1976, the incidence rate had fallen to 0.08 per 100 000 population.[1] In 1989, a World Health Organisation (WHO) meeting endorsed a recommendation that envisaged full control of diphtheria throughout Europe by 1995.[2] Contrary to this optimistic prediction by international experts, 1990 saw the beginning of a diphtheria outbreak in Russia that rapidly spread throughout the newly independent states of the former Soviet Union and by 1995 a total of 47 808 cases had been reported.[1]

The Baltic countries were not spared. The paper by Logina and Donaghy (this issue, pp 433–8) reports on the diphtheria epidemic that swept through Latvia in 1994 to 1996, affecting a total of 731 people, mostly adults aged 30 to 50 years. Neurological complications, especially diphtheric polyneuropathy, were found in about 15% of patients admitted to hospital. This coincidence provided the opportunity for a detailed study of 50 patients with diphtheric neuropathy. The authors remind the readership of the typical biphasic disease course of diphtheric polyneuritis, with the characteristic early bulbar dysfunction due to toxic paralysis of the soft palate and pharyngeal muscles, followed by the delayed onset of other cranial nerve palsies and often a generalised peripheral neuropathy. Neurological and cardiac complications were particularly common in patients with severe faucial diphtheria. The paper further emphasises the importance of administering antitoxin as soon as the diagnosis of diphtheria is suspected, without waiting for culture confirmation. Effectiveness of the anti-toxin can only be expected as long as the toxin has not yet bound to tissues— that is, within the first 2 days from onset of symptoms. As diphtheria antitoxin is derived from horses, appropriate precautions and sensitivity skin testing should be performed before its administration.

The reasons for this resurgent diphtheria epidemic are not fully understood. Major contributing factors were economic hardship, crowding due to large urban migration, and failing health systems as a result of the dissolution of the Soviet Union. Consequently, low vaccination coverage and inappropriate primary vaccination practices led to the presence of many susceptible children. Moreover, as vaccine induced immunity wanes over time unless periodic boosters are administered every 10 years, many adults had again become susceptible to the disease. Before the vaccine era, most persons had acquired natural lifelong immunity in childhood through exposure to *C diphtheriae*. Thus the susceptibility of adults to diphtheria is a new phenomenon of the vaccine era. Serological studies in the United Kingdom, Germany, newly independent states of the former Soviet Union, and in the United States indicate that 20% to 50% of adults aged>20 years are susceptible to diphtheria.[2–5] These studies showed a significant trend of decreasing immunity with increasing age, resulting in lack of protection, particularly for adults aged 30 to 50 years. This potential risk assumes a particular significance in today's international travel. The WHO Advisory Committee on Immunisation Practices recommends that all children receive routine vaccination with a series of five doses of DTP at ages 2, 4, 6, and 12–15 months and 4 to 6 years; booster diphtheria-tetanus immunisations should then be administered every 10 years. Persons travelling to areas with diphtheria activity should have completed the primary series and should have received a dose of vaccine within the previous 10 years.

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EDITORIAL COMMENTARY

From mystery to prevention: sudden unexpected death in epilepsy, time to move on

This noteworthy paper of Kloster and Engelskohn in this issue (pp 439–44) supports an important hypothesis in relation to the cause of sudden unexpected death in epilepsy (SUDEP)—namely, that SUDEP is largely seizure related. Their finding of a preponderance of the prone position of the body is also of interest and may have a bearing on proposed mechanisms as well as the potential for the prevention of these deaths.

But firstly, certain methodological aspects should be noted. The control group of non-SUDEP deceased epilepsy cases is not appropriate for all variables studied. Epilepsy diagnosis is an example. The non-SUDEP group would include cases dying of the underlying condition causing or associated with the epilepsy and is expected to include more symptomatic cases. The authors do not define the terms used with regard to epilepsy diagnosis, in particular idiopathic epilepsy,[1] which has had a different meaning in epidemiological studies to that in the International League against Epilepsy (ILAE) classification. Some caution is required in interpreting the interesting cardiac and neuropathological findings unavoidably performed in different units without a predefined protocol and presumably differing levels of expertise. The severity of epilepsy, from the point of view of safety and mortality, cannot be equated with seizure frequency, as seizure type and severity are at least equally relevant if not more so. Importantly, the authors, having selected a relatively strict definition of SUDEP, apply it rather liberally. Readers may take issue with the inclusion of a few cases (such as with severe hyponatraemia and chest pain requiring ECG before death). My intention is not to downplay other mechanisms or associated conditions important in individual cases and, more generally, likely to be particularly relevant among elderly patients. The intention is to emphasise that the category of SUDEP, a significant one in proportional mortality studies, is intended to include only those where the history and postmortem findings do not suggest alternative pathology.

Nevertheless, this is a very useful study with valid conclusions. The findings support previous evidence suggesting that most of these deaths are seizure related. This view is widely subscribed to by United Kingdom based workers, but has met with resistance elsewhere, particularly across the Atlantic. Although keeping an open mind is at times admirable, in this situation, an attachment to the mystery of the unexplained, has only served to constrain efforts at prevention. Whereas seizures may not be the only cause of SUDEP, they are the cause of most cases.

Another particularly interesting discussion in this report relates to the finding of a more commonly found prone position among SUDEP cases than would be expected by chance. Although not subscribing to the simplistic notion of attributing nocturnal epilepsy deaths to suffocation face down alone, if the various factors leading to hypoxia during generalised convulsive seizures are considered, position is yet another factor that could contribute to a fatal outcome. This is in addition to central ictal and postictal hypoventilation, pulmonary oedema, excessive secretions, and postictal coma. Central and obstructive apnoea (whether intrinsic or extrinsic) are potentially amenable to intervention by stimulating and positioning the patient. A simple answer will not prevent all cases, but aggressive treatment of the epilepsy, particularly prevention of generalised convulsions, and the presence of a person capable of giving assistance in the event of a seizure are likely to prevent some of these deaths. The first has implications to service provision, optimal medical treatment of the epilepsy, and patient education, the second to supervision with its attendant limitations. The first translates to better health care, the second to informed choice.[2]

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